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Poly(β-malic acid) derivatives with unsaturated lateral groups: epoxidation as model reaction of the double bonds reactivity

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Abstract

Poly(β-malic acid) derivatives bearing a lateral allyl or 3-methyl-3-butenyl ester group have been prepared by anionic ring opening polymerization or copolymerization of 4-allyloxycarbonyl-2-oxetanone or 4-[3-methyl-3-butenyloxycarbonyl]-2-oxetanone and 4-benzyloxycarbonyl-2-oxetanone as comonomer. These new chiral β-substituted-β-lactones with unsaturated lateral groups have been synthesized from aspartic acid as precursor and by using allylic alcohol or 3-methyl-3-buten-1-ol for opening bromosuccinic acid anhydride, an intermediate compound in the monomer synthesis route. The proportion of unsaturated lateral groups in the polymer was strictly controlled by the proportion of the corresponding lactone in the initial monomers mixture and can vary up to 100%. Functionalized polyesters have been prepared and characterized, and to test the reactivity of the present double bonds, epoxidation has been carried out by using *m*-chloroperbenzoic acid and dimethyldioxirane as chemical reagents. The activation of the double bond was depending on its chemical environment and on the polymer composition, but quantitative epoxidation has been achieved.

Keywords: Allyl malolactonate; 3-Methyl-3-butenyl malolactonate; Poly(3-alkenyl-β-malic acid esters); Epoxidation

1. Introduction

The development of synthetic biodegradable polymers is particularly important in the field of temporary therapeutic applications. Besides surgical devices like sutures, absorbable plates, drug delivery systems have been developed by using polymeric materials combining glycolic acid and lactic acid enantiomers repeating units with a composition and a distribution depending on the specific applications [1].

At present time, many investigations are carried out on the design of bioactive molecules carrier systems corresponding to required material properties [2]. The bioactive molecules can be drugs, antifouling substances, herbicides, weed-killers and the polymeric carrier has to be adapted to prerequisites like hydrophilicity/hydrophobicity, permeability, degradation rate, targeting [3]. In many cases, tailor-making of multimeric polymers is necessary and versatility of the polymeric material for obtaining desirable intrinsic properties requires functional lateral groups to which bioactive, specific, neutral, chiral or reactive molecules are covalently attached [4]. Therefore, polymers with hydrolysable backbone and lateral functional groups have been selected: poly(amino acids),

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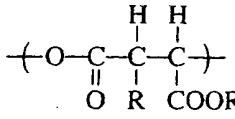
polyesteramides and polyesters [5]. Poly(β-malic acid), a polyester with lateral carboxy groups and a stereogenic center in the monomer unit, is the parent compound of a large family including tailor-making derivatives based on the possibility for varying the nature of the lateral ester group [6] (neutral, chiral, bioactive) or for varying the structure of the main chain by introducing an alkyl group and accordingly a second stereogenic group in the repeating monomer unit [7]. Hydrophilicity of these materials is obtained by selective catalytic hydrogenolysis of the benzyl protecting groups ($R'=CH_2C_6H_5$) present in the macromolecular chain [8].



R = H or alkyl

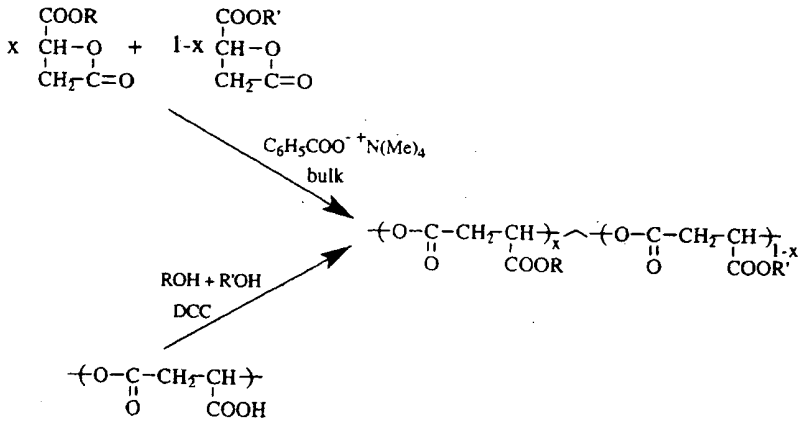
R' = H or variable group

poly(β-malic acid) derivatives

These polymers are accessible by chemical synthesis routes starting from racemic or optically active aspartic acid [9], 3-alkylaspartic acid [10] or malic acid [11] and anionic ring opening polymerization or copolymerization of suitable β-substituted-β-lactones [12], or by biological synthesis [13] using different microorganisms connected to chemical modifications (Scheme 1).

The chemical route appears very versatile as it opens the way to a large number of racemic or optically active derivatives by changing the chemical structure and the proportions of the esters groups [14]. The introduction of lateral double bonds in these polyesters is important in regard to chemical activation and chemical modification for coupling as crosslinking with a view to design artificial biopolymers, degradable hydrogels and delivery systems. These unsaturated lateral groups can be activated by different chemical processes as radical or epoxidation reactions.

In this paper, we wish to report the synthesis and the characterization of β-substituted-β-lactones with unsaturated pendant groups by the aspartic route: 4-allyloxycarbonyl-2-oxetanone (allyl malolactonate) and 4-[3-methyl-3-butenyloxycarbonyl]-2-oxetanone (3-methyl-3-butenyl malolactonate). These new malolactonic acid esters have been polymerized or copolymerized with benzyl malolactonate conducting to high molecular weight functionalized polyesters. In order to test the reactivity of the unsaturated pendant groups, their epoxidation has been carried out; the interest of such activated structures yields in the possibility of further chemical transformation leading to biodegradable polymeric systems for temporary therapeutic or biological applications.



Scheme 1. Synthesis of poly(β-malic acid esters) derivatives.

2. Experimental part

2.1. Chemicals

Methylene chloride was previously purified by distillation under CaH_2.

m-Chloroperbenzoic acid (MCPBA) was purified by dissolution in methylene chloride, dried under magnesium sulfate and concentrated.

Other chemicals were purchased from Janssen Chemical.

2.2. Synthesis of lactones

2.2.1. Preparation of benzylmalolactonate (1a)

Benzylmalolactonate was synthesized by using the aspartic acid route previously described [7].

2.2.2. Preparation of allyl malolactonate (1b)

To an ice-cold mixture of L-aspartic acid (100 g) and NaBr (416 g) in H_2SO_4 (2 *N*) (1680 ml), $NaNO_2$ (62 g) was added progressively over a period of 1.5 h. The whole mixture was further stirred for 30 min at room temperature. After addition of urea (8 g) to decompose the excess reagent, bromosuccinic acid was extracted with ethyl acetate. The combined extracts were washed with slightly acidic water and dried over anhydrous sodium sulfate. Crude bromosuccinic acid was recrystallized four times in acetonitrile, (yield 60%, mp 175°C).

Bromosuccinic acid (50 g) was dried under vacuum at 40°C for 4 h, then dissolved in anhydrous tetrahydrofurane (125 ml). Trifluoroacetic acid anhydride, TFAA, (1.2 parts, 43 ml) was added and the suspension was stirred magnetically at room temperature for 2 h. Trifluoroacetic acid resulting of the reaction and TFAA excess were removed by vacuum distillation at room temperature to conduct to bromosuccinic acid anhydride as a white solid with a quantitative yield. It is immediately kept under nitrogen atmosphere. Allyl alcohol (17.9 ml, 1 eq) was added to the white solid and the mixture was kept overnight 22 h) at 60°C (yield 98%).

The resulting mixture was dissolved in water (250 ml) and sodium hydroxide was added to rise pH up to 7.8. CH_2Cl_2 (500 ml) was introduced in the round bottom flask and the biphasic system was allowed to stir 5 h. at 40°C. After cooling, the organic layer was separated from the aqueous phase and dried under $MgSO_4$.

The allyl malolactonate was purified by chromatography on silica gel (petroleum ether/ethyl ether: 4/6) and distilled three times under vacuum (yield 19% from lactonisable ester).

^{1}H NMR (90 MHz, $CDCl_3$, δ ppm): 4.02–3.17 (dq, 2H, CH_2 lactone); 4.70–4.50 (m, 2H, CH_2 allyl); 5.16–5.03 (dd, 1H, CH lactone); 5.46–5.27 (m, 2H, $=CH_2$); 6.17–6.74 (m, 1H, =CH).

^{13}C NMR (2.25 MHz, $CDCl_3$, δ ppm); 43.32 (CH_2 lactone); 65.18 (CH lactone); 66.51 (CH_2-CO_2); 119.52 ($=CH_2$); 130.79 (CH=); 167.73 (C=O).

2.2.3. Preparation of 3-methyl-3-butenyl malolactonate (1c)

3-Methyl-3-butenyl malolactonate was prepared as described above. 25.6 ml (1 eq) of 3-methyl-3-buten-1-ol were added to the bromosuccinic acid anhydride and the mixture was kept overnight (22 h) at 60°C (yield 95%). The lactonisation reaction was carried out 3 h at 40°C to give the 3-methyl-3-butenyl malolactonate. This lactone was purified by chromatography on silica gel with chloroform and then distilled three times under vacuum (yield 19% from lactonisable ester).

^{1}H NMR (90 MHz, $CDCl_3$, δ ppm): 1.76 (s, 3H, CH_3); 2.40 (t, 2H, $CH_2-C=$); 3.40–4.17 (dq, 2H, CH_2 lactone); 4.24–4.49 (t, 2H, $COO-CH_2$); 4.76 (m, 2H, $=CH_2$); 4.96–5.08 (dd, 1H, CH lactone).

^{13}C NMR (2.25 MHz, $CDCl_3$, δ ppm): 22.17 (CH_3); 36.44 ($CH_2-C=$); 43.43 (CH_2 lactone); 63.99 ($COO-CH_2$); 65.21 (CH lactone); 112.75 ($=CH_2$); 140.89 (C=); 165.78 (C=O); 168.08 (C=O).

2.3. Preparation of polymers 2a, 2b, 2c, 2d

Polymers and copolymers were synthesized by anionic ring opening polymerization in bulk with tetraethylammonium benzoate (10^{-3} eq) as

initiator. 10^{-3} part of tetraethylammonium benzoate was dried under vacuum for 2 h and kept under nitrogen; malolactonate or a mixture of malolactonates was added to the initiator under nitrogen atmosphere and the mixture was kept at 37°C until no more lactone was present (IR control). Polymer was then dissolved in acetone and one drop of concentrated HCl was added. Polymer was precipitated with ethanol and dried under vacuum.

2.3.1. Poly(allyl malolactone) PMLA Al (2a)

T_g = −4°C, SEC (dioxane, PS standard): M_n = 62200; M_w = 34100; I_p = 1.83; M_{SEC} = 78700.

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.95 (s, 2H, CH_2 main chain); 4.61 (d, 2H, $COO-CH_2$); 5.20–5.42 (dd, 2H, $=CH_2$); 5.54 (large s, 1H, CH main chain); 5.70–6.10 (m, 1H, CH=).

^{13}C NMR (22.5 MHz, $CDCl_3$, δ ppm): 35.52 (CH_2 main chain); 66.35 ($COO-CH_2$); 68.57 (CH main chain); 119.03 ($=CH_2$); 131.30 (CH=); 112.75, 167.76 (C=O); 168.08 (C=O).

2.3.2. Poly(benzyl malolactonate-co-allyl malolactonate) PMLA Be-Al (2b)

T_g = +2°C, SEC (dioxane, PS standard): M_n = 86800; M_w = 41600; I_p = 2.08; M_{SEC} = 104200.

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.95 (s, 2H, CH_2 main chain); 4.59 (s, 0.3 × 2H, CH_2 allylic); 5.12 (s, 0.7 × 2H, $CH_2-C_6H_5$); 5.21 (m, 1H, 0.3 × 2H, $=CH_2$); 5.30 (s, 0.3 × H, CH=); 5.51 (s, 1H, CH main chain); 7.28 (d, 0.7 × 5H, C_6H_5).

^{13}C NMR (22.5 MHz, $CDCl_3$, δ ppm): 35.50 (CH_2 main chain); 66.37 ($COO-CH_2$); 67.56 ($CH_2C_6H_5$); 68.65 (CH main chain); 119.03 ($=CH_2$); 128.24–128.68 (C_6H_5); 131.33 (CH=); 167.81 (C=O); 168.14 (C=O).

2.3.3. Poly(3-methyl-3-butenyl malolactonate) PMLA MeBu (2c)

T_g = −14.6°C, SEC (dioxane, PS standard): M_n = 32300; M_w = 61400; I_p = 1.9; M_{SEC} = 64800.

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 1.76 (s, 3H, CH_3); 2.39 (t, 2H, $CH_2-C=$); 3.05 (m, 2H, CH_2 main chain); 4.29 (t, 2H, $COO-CH_2$); 4.79 (s, 2H, $=CH_2$); 5.50 (t, 1H, CH main chain).

^{13}C NMR (22.5 MHz, $CDCl_3$, δ ppm): 22.98 (CH_3); 36.69 (CH_2 main chain); 37.64 ($COO-CH_2$); 64.91 ($CH_2-C=$); 69.95 (CH main chain); 113.40 ($=CH_2$); 142.98 (C=); 169.23 (C=O); 169.44 (C=O).

2.3.4. Poly(benzyl malolactonate-co-3-methyl-3-butenyl malolactone) PMLA Be-co-MeBu (2d)

T_g = +15°C, SEC (dioxane, PS standard): M_n = 40300; M_w = 80700; I_p = 2.0; M_{SEC} = 79400.

^{1}H NMR (90 MHz, $CDCl_3$, δ ppm): 1.69 (s, 0.9 × H, CH_3); 2.32 (t, 0.3 × 2H, $CH_2-C=$); 2.98 (s, 2H, CH_2 main chain); 4.22 (t, 2H, $COO-CH_2$); 4.74 (s, 0.3 × 2H, $=CH_2$); 5.15 (s, 0.7 × 2H, CH main chain).

^{13}C NMR (22.5 MHz, $CDCl_3$, δ ppm): 22.33 (CH_3); 35.44 (CH_2 main chain); 36.47 ($COO-CH_2$); 63.38 ($CH_2-C=$); 67.33 ($CH_2-C_6H_5$); 69.60 (CH main chain); 112.64 ($=CH_2$); 129.51–129.62 (C_6H_5); 141.08 (C=); 169.14 (C=O); 169.44 (C=O).

2.4. Epoxidation of polymers

2.4.1. Synthesis of poly(benzyl malolactonate-co-2,3-epoxypropyl malolactonate) (3b)

367 mg of PMLA (Be-*co*-Al) were dissolved in 3 ml of purified methylene chloride. Under nitrogen atmosphere, 214 mg of MCPBA (2 eq) in 2 ml of methylene chloride were added. The mixture was kept under stirring at room temperature until a white precipitate appeared. After filtration, the epoxidized polymer was precipitated in ethanol and dried under vacuum for 2 days at room temperature.

^{1}H NMR (90 MHz, $CDCl_3$, δ ppm): 2.81–2.58 (d, 0.3 × 2H, CH_2 oxirane); 2.97 (s, 2H, CH_2 main chain); 4.02–4.09 (d, 0.3 × 2H, $COOCH_2$); 4.46–4.60 (m, 0.3 × H, CH oxirane); 5.14 (s, 0.7 × 2H, $CH_2-C_6H_5$); 5.59 (s, 1H, CH main chain); 7.28 (d, 5 × 0.7H, C_6H_5).

^{13}C NMR (22.5 MHz, $CDCl_3$, δ ppm): 35.44 (CH_2 main chain); 44.51 (CH_2 oxirane); 48.90 (CH oxirane); 66.29 ($COOCH_2$); 68.59 ($CH_2-C_6H_5$); 68.62 (CH main chain); 118.67–118.24 and 135.03 (C_6H_5); 167.97 and 168.16 (C=O).

IR (ν, cm^{-1}): 910, 1260, 1380, 3050 (oxirane).

2.4.2. Synthesis of poly(3-methyl-3,4-epoxybutyl malolactonate) (3c), and poly(benzyl malolactonate-co-3-methyl-3,4-epoxybutyl malolactonate) (3d)

Epoxidation of PMLA MeBu (**2c**) and PMLA (Be-*co*-MeBu) (**2d**) was conducted with the same procedure as described below.

(3c): ^1H NMR (90 MHz, $CDCl_3$, δ ppm): 1.33 (s, 3H, CH_3); 1.87–2.03 (m, 2H, $O-CH_2-CH_2$); 2.66–2.58 (d, 2H, CH_2 epoxy); 2.97–3.10 (d, 2H, CH_2 main chain); 4.29 (t, 2H, $COOCH_2$); 5.56 (s, 1H, CH main chain).

^{13}C NMR (22.5 MHz, CD_3OCD_3, δ ppm): 21.90 (CH_3); 36.48 (CH_2 main chain); 54.03 (CH_2 epoxy); 55.57 (C epoxy); 63.59 ($COO-CH_2CH_2$); 68.46 (CH main chain); 169.55–169.25 (C=O).

IR (ν, cm^{-1}): 910, 1260, 1380, 3050 (epoxy), 1740 (C=O ester).

(3d): ^1H NMR (90 MHz, $CDCl_3$, δ ppm): 1.33 (s, 3 × 0.3H, CH_3); 1.87–2.03 (m, 0.3 × 2H, $O-CH_2-CH_2$); 2.66–2.58 (d, 0.3 × 2H, CH_2 epoxy); 2.97–3.10 (d, 2H, CH_2 main chain); 4.29 (t, 0.3 × 2H, $COOCH_2$); 5.14 (s, 0.7 × 2H, $CH_2-C_6H_5$); 5.59 (s, 1H, CH main chain).

^{13}C NMR (22.5 MHz, CD_3OCD_3, δ ppm): 21.90 (CH_3); 36.48 (CH_2 main chain); 54.03 (CH_2 epoxy); 55.57 (C epoxy); 63.59 ($COO-CH_2CH_2$); 68.46 (CH main chain); 68.59 ($CH_2-C_6H_5$); 118.67–118.24 and 135.03 (C_6H_5); 169.55–169.25 (C=O).

IR (ν, cm^{-1}): 910, 1260, 1380, 3050 (epoxy), 1740 (C=O ester).

2.4.3. Epoxidation of 3a

Preparation of a 0.1-M dimethyldioxirane (DMD) solution. In a thin round bottom flask, 54 ml of water, 42 ml of acetone and 12.5 g of $NaHCO_3$ were introduced, 25.5 g of caroate were slowly added. The solution was kept under 100 mbars vacuum and DMD in acetone was condensed at −40°C. 0.1 g of poly(allyl β-malate) was dissolved in purified methylene chloride and 30 ml of the previous solution were added. The mixture was kept under stirring at room temperature for 24 h. 30 ml of the DMD solution were added and the mixture was again kept at room temperature for 24 h. After filtration, the epoxidized polymer was precipitated with ethanol.

$T_g = 11.5$°C.

^1H NMR (90 MHz, $CDCl_3$, δ ppm): 2.83–2.68 (d, 2H, CH_2 epoxy); 2.97–3.10 (s, 2H, CH_2 main chain); 4.02–4.09 (d, 2H, $COOCH_2$); 4.46–4.60 (m, H, CH epoxy); 5.56 (s, 1H, main chain).

^{13}C NMR (22.5 MHz, $CDCl_3$, δ ppm): 35.47 (CH_2 main chain); 44.43 (CH_2 epoxy); 48.95 (CH epoxy); 66.40 ($COOCH_2$); 68.46 (CH main chain); 167.87 (C=O).

IR (ν, cm^{-1}): 910, 1260, 1380, 3050 (epoxy).

2.5. Hydrogenolysis of copolymers

2.5.1. Hydrogenolysis of 3b

Poly(β-malic acid-*co*-2,3-epoxypropyl-β-malate) (30/70), (**4b**), was obtained by the catalytic hydrogenolysis of **3b**. After dissolution of the 250 mg polymer in dioxane (5 ml), 50 mg (20% weight) of palladium were added and the hydrogenolysis was conducted with hydrogen at room temperature during 24 h. **4b** was obtained after filtration over celite, evaporation of the dioxane and dried under vacuum.

Yield = 100%; $T_g = 47$°C.

^1H NMR (90 MHz, CDCOD, δ ppm): 2.81–2.58 (d, 0.3 × 2H, CH_2 epoxy); 2.97 (large s, 2H, CH_2 main chain); 4.02–4.09 (d, 0.3 × 2H, $COOCH_2$); 4.46–4.60 (m, 0.3H, CH epoxy); 5.59 (large s, 1H, CH main chain); 7.28 (d, 5 × 0.7H, C_6H_5).

^{13}C NMR (22.5 MHz, CD_3OD, δ ppm): 37.3 (CH_2 main chain); 44.5 (CH_2 epoxy); 48.90 (CH epoxy); 66.29 ($COOCH_2$); 68.80 (CH main chain); 170.72 (C=O carboxylic acid); 172.84 (C=O ester).

IR (ν, cm^{-1}): 910, 1260, 1380, 3050 (epoxy); 1638 (C=O carboxylic acid); 1740 (C=O ester).

2.5.2. Hydrogenolysis of 3d

Poly(β-malic acid-*co*-3,4-epoxy-3-methylbutyl-β-malate) (30/70) was obtained by the catalytic hydrogenolysis of **3d** as described before.

Yield = 100%

^{1}H NMR (90 MHz, CD_3OD, δ ppm): 1.33 (s, 0.3 × 3H, CH_3); 1.87–2.03 (m, 0.3 × 2H, $O-CH_2-CH_2$); 2.66–2.58 (d, 0.3 × 2H, CH_2 epoxy); 63.59 ($COO-CH_2-CH_2$); 68.46 (CH main chain); 170.70 (C=O carboxylic acid); 172.80 (C=O ester).

^{1}H NMR (90 MHz, CDCOD, δ ppm): 2.81–2.58 (d, 0.3 × 2H, CH_2 epoxy); 2.97 (large s, 2H, CH_2 main chain); 4.02–4.09 (d, 0.3 × 2H, $COOCH_2$); 4.46–4.60 (m, 0.3H, CH epoxy); 5.59 (large s, 1H, CH main chain); 7.28 (d, 5 × 0.7H, C_6H_5).

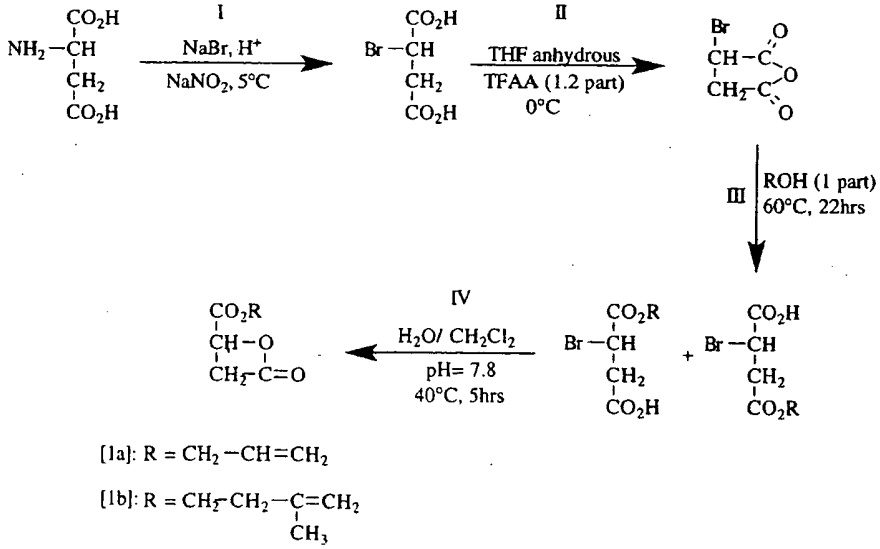
^{13}C NMR (22.5 MHz, CD_3OD, δ ppm): 37.3 (CH_2 main chain); 44.52 (CH_2 epoxy); 48.90 (CH epoxy); 66.29 ($COOCH_2$); 68.85 (CH main chain); 170.75 (C=O carboxylic acid); 172.82 (C=O ester).

IR (ν, cm^{-1}): 910, 1260, 1380, 3050 (epoxy); 1638 (C=O carboxylic acid); 1740 (C=O ester).

3. Results and discussion

The first attempt to prepare 4-allyloxycarbonyl-2-oxetanone (allyl malolactonate) was carried out by using the ketene route consisting of the base catalyzed 2+2 cycloaddition between ketene and allyl glyoxalate as in the case of alkyl malolactonate formation [15]. The critical stage was the dehydratation of glyoxalic acid ester and the yield of lactonization was very low and insufficient for further purification and polymerization.

The different steps of the monomer synthesis route appear on Scheme 2. This preparation has also been used for 4-[3-methyl-3-butenyloxycarbonyl]-2-oxetanone (3-methyl-3-butenyl malolactonate). The limitation for the synthesis of this type of β-substituted-β-lactone is the nucleophilicity of the alcohol towards bromosuccinic



[1a]: R = $CH_2-CH=CH_2$

[1b]: R = $CH_2-CH_2-C(CH_3)=CH_2$

Scheme 2. Synthesis of allyl malolactonate (**1a**) and 3-methyl-3-butenyl malolactonate (**1b**).

acid anhydride. Allyl alcohol and 3-methyl-3-buten-1-ol were reactive and have conducted to a 70/30 mixture of corresponding monobromosuccinic acid esters, the major product being lactonizable.

Yields of the ring closure reaction were equivalent to these observed in the formation of benzyl malolactonate (65% from the efficient monoester). Purification of the two malolactones were conducted with the care as generally: chromatography and distillation. Purified products were transparent liquids and can be stocked.

These monomers have been polymerized or copolymerized in the presence of benzyl malolactonate in a molar ratio (30/70). The polymerization reactions were carried out in bulk, at 37°C, in the presence of tetraethylammonium benzoate as initiator and processed by anionic ring opening with configuration inversion of the asymmetric carbon [13]. Table 1 displays that high molecular weight polymeric materials can be prepared. As in the case of the different poly(β-malic acid) derivatives, transfer reactions must be involved; theoretical molecular weights were different from the experimental ones.

Polydispersity was, in all cases, close to two. The solubility of the racemic polymeric materials containing 3-methyl-1-butenyl esters as lateral groups was identical to that of racemic poly(benzyl β-malate), PMLA Be, in the current organic solvents (acetone, tetrahydrofurane, chloroform, dichloromethane), contrarily to copolymers and homopolymers with allyl esters lateral groups which were not soluble in acetone. Homopolymers and copolymers were amorphous and T_g were inferior to the ambient temperature (T_g (PMLA Be) 37°C).

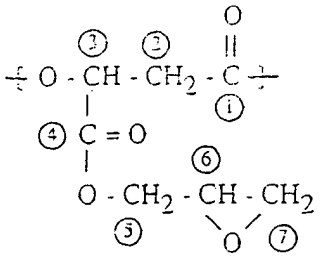
Taking into account the difficulties for obtaining malolactonates and the corresponding polymers or copolymers with lateral activating groups from *N*-hydrosuccinimide, benzotriazole, trichlorophenol, *p*-nitrophenol, by using the synthesis route starting from aspartic acid, a substitution strategy was consisting in the introduction of lateral unsaturated groups and in their further chemical modification. The double bond is not activating but after epoxidation, it becomes very reactive for attaching or crosslinking. Two chemical reagents have been used for this reaction: *m*-chloroperbenzoic acid (MPCBA) and dimethyldioxirane (DMD). Epoxidation reactions of the different polymer materials (Scheme 3) were investigated by ^{13}C NMR; signals at 119.5 and 130.8 ppm in allyl group and 112.6 and 141.1 ppm in 3-methyl-3-butyl group disappeared during epoxidation reaction and two new peaks at respectively 48.9 and 44.5 ppm, 54.0 and 55.6 ppm appeared, characteristic of the oxirane group.

MPCBA is commercial, not very aggressive, selective and very easy to use; epoxidation was carried out at room temperature in anhydrous dichloromethane. For poly(allyl β-malate), best results were obtained with two equivalents of

Table 1
Characteristics of poly(β-malic acid) derivatives

Polymers	M_n	M_p	M_{SEC}	M_{th}	T_g (°C)	I_p
PMLA Be	61000	110000	174000	206000	37	1.8
PMLA Al	34000	62200	78700	156000	−4	1.8
PMLA MeBu	32000	61400	64800	184000	−15	1.9
PMLA (Be-*co*-Al) (70/30)	41700	86800	104200	177000	2	2.1
PMLA (Be-*co*-MeBu) (70/30)	40300	80700	79400	182000	+15	2.0

SEC: polymers solutions in dioxane with polystyrene as standards.
PMLA Be: poly(benzyl-β-malate);
PMLA Al: (poly(allyl β-malate);
PMLA MeBu: poly(3-methyl-3-butenyl β-malate);
PMLA (Be-*co*-Al): PMLA (benzyl β-malate-*co*-allyl β-malate).
PMLA (Be-*co*-MeBu): poly(benzyl β-malate-*co*-3-methyl-3-butenyl β-malate).



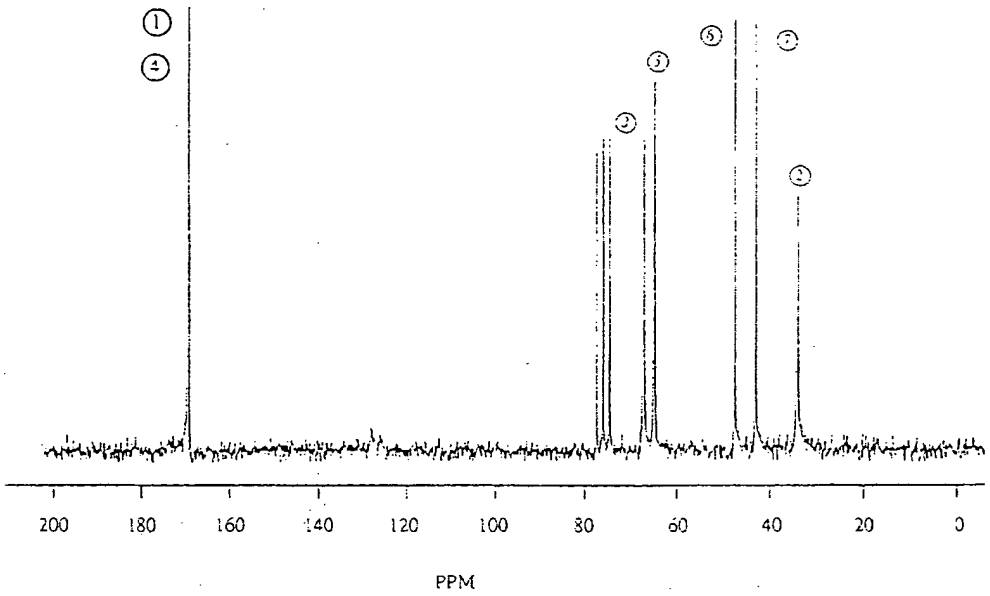
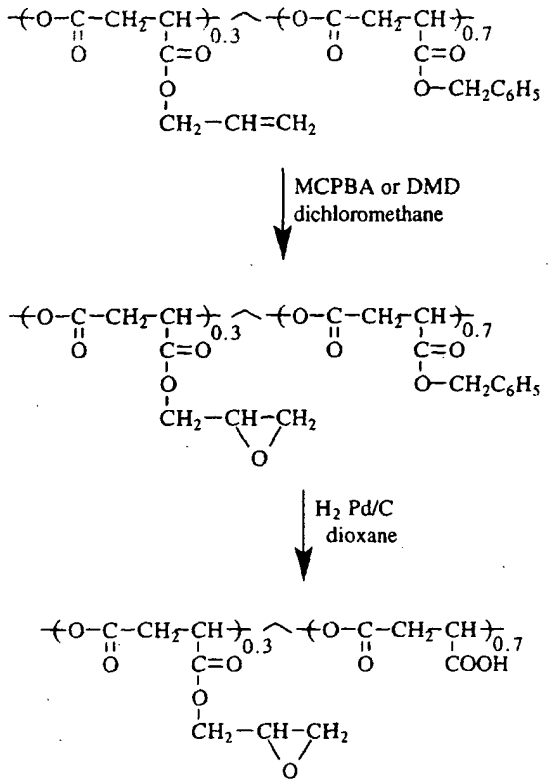


Fig. 1. ^{13}C-NMR spectrum of poly(2,3-epoxypropyl β-malate) in $CDCl_3$

epoxidation reagents (10 days, yield 40%). With poly(benzyl β-malate-*co*-allyl β-malate) (70/30), the reaction was complete in four days with two equivalents of MPCBA. Total epoxidation of poly(allyl β-malate) was carried out by using dimethyldioxirane (6 eq, 24 h); resulting poly(2,3-epoxypropyl β-malate) was soluble in the same solvents that in the case of PMLA Al except tetrahydrofuran. With MCPBA, epoxidation of PMLA MeBu and PMLA Be-*co*-MeBu (70/30) was quantitative (Table 2). Furthermore, solubility of epoxidized polymers in organic solvents show crosslinking reaction does not occur during the epoxidation.

Fig. 1 displays ^{13}C-NMR spectrum of poly(allyl β-malate) after epoxidation reaction. Besides the disappearance of the 2 peaks corresponding to unsaturated carbons, the spectrum displayed two new signals corresponding to the two carbons of the oxirane group, no new other carbon atoms peaks appeared and we can conclude for the four compounds, this reaction is main chain respecting. Further specific catalytic hydrogenolysis of the protecting benzyl groups



Scheme 3. Synthesis of poly(β-malic acid-*co*-2,3-epoxypropyl-β-malate) (70/30)

has been carried out on the two copolymers in dioxane and ^{1}H-NMR spectra displayed the complete disappearance of signals corresponding to benzyl protons. The resulting copolymers are water soluble, due to the presence of free carboxylic acid groups.

4. Conclusions

The spectrum of available malolactonic acid esters has been expanded to compounds with functional lateral groups as unsaturated ester groups. It has been shown, all double bonds contained in corresponding polyesters could be epoxidized without crosslinking, even in the case of allylic lateral groups. Tailor-made bioartificial polyesters, bearing three different functionalized lateral groups after opening and chemical modification of the epoxy groups, are under biological study as heparansulfate-like.

Table 2
Epoxidation reactions of poly(β-malic acid) derivatives

Polymers	Reagents (parts)	Reaction time (in days)	Yield (%)
PMLA Al	MCPBA (2)	10	40
PMLA MeBu	MCPBA (1.3)	1.5	100
PMLA (Be-*co*-Al) (70/30)	MCPBA (2)	4	100
PMLA (Be-*co*-MeBu) (70/30)	MCPBA (1.3)	1.5	100
PMLA Al	DMD (6)	1	100

MCPBA: metachloroperbenzoic acid.
DMD: dimethyldioxirane.

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